



# CHEMISTRY 4000

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Topic #6: Formation of Cyclic Structures

Spring 2022

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# Strategies for Making Carbocycles

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- There are three strategies worth considering when a synthetic target contains one or more carbocycles (rings containing only carbon atoms).
  - Use reactants already containing a carbocycle of the required size. Reactions may be necessary to obtain the desired level of saturation.
  - Use a one-bond disconnection in the same way that you would for formation of chains or branched structures.
  - Use a two-bond disconnection corresponding to a cycloaddition reaction.
    - Cycloadditions involving  $4n+2$   $\pi$  electrons are thermally allowed. e.g. Diels-Alder reactions are [4+2] cycloadditions (6  $\pi$  electrons)
    - Cycloadditions involving  $4n$   $\pi$  electrons are photochemically allowed. e.g. [2+2] cycloadditions involve 4  $\pi$  electrons and require light



# Strategies for Making Cyclopropanes

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- When applying a one-bond disconnection to a cyclopropane ring, we use a functional group oriented approach.
- The only difference between this challenge and elongation of a carbon chain by the same approach is that, here, the nucleophilic carbon and the electrophilic carbon are on the same molecule and separated by just one carbon:



# Strategies for Making Cyclopropanes

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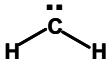


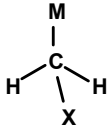
- While cyclopropane rings are strained, their formation is kinetically favoured. Why?

# Strategies for Making Cyclopropanes



- When applying a two-bond disconnection to a cyclopropane ring, we find that we need an alkene and a carbenoid reagent.

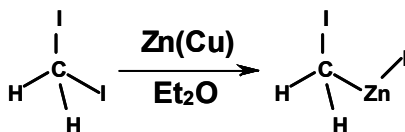
-  is carbene. It is \*highly\* reactive and would react with an alkene to give a cyclopropane. It would also react with just about anything else in its path...

-  is a carbenoid reagent. It is electrophilic because of the leaving group X (just as the carbene is electrophilic because of the carbon's incomplete octet). The electrons in the C-M bond are nucleophilic (just as the lone pair of the carbene is nucleophilic).

# Strategies for Making Cyclopropanes



- One of the simplest carbenoid reagents is generated in the Simmons-Smith reaction. Diiodomethane is treated with copper-activated zinc to give  $\text{H}_2\text{C}(\text{I})\text{ZnI}$ :



- This carbenoid reacts with an alkene to give the corresponding cyclopropane (with preservation of relative stereochemistry):
- In cases where this approach gives low yields, diiodomethane can be treated with diethylzinc and trifluoroacetic acid instead, giving  $\text{H}_2\text{C}(\text{I})\text{Zn}(\text{O}_2\text{CCF}_3)$  which reacts in the same way as  $\text{H}_2\text{C}(\text{I})\text{ZnI}$



# Strategies for Making Cyclobutanes



- For a one-bond disconnection in a cyclobutane ring, we might think of a functional group oriented approach similar to that on page 3:
  
- Unfortunately, it wouldn't work. We'd mostly get intermolecular reaction not intramolecular reaction. The problem is that four-atom rings are neither kinetically nor thermodynamically favoured. Why not?



# Strategies for Making Cyclobutanes



- When applying a two-bond disconnection to a cyclobutane ring, we find that we need two alkenes as the starting materials:
- We know from studying the Diels-Alder reaction in CHEM 2600 that a cycloaddition reaction requires that the HOMO of one reagent and the LUMO of the other reagent must be able to combine in phase at both ends simultaneously. What do the HOMO and LUMO of ethene look like?





# Strategies for Making Cyclobutanes



- What happens to the HOMO and LUMO of a molecule of ethene when a photon excites an electron?
- Often, catalytic amounts of a photosensitizer are included to facilitate absorption of the photon and excitation of the electron. 9



# Strategies for Making Cyclobutanes

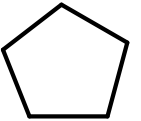
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- In a [2+2] cycloaddition, the relative stereochemistry of groups about each double bond is preserved. If both alkenes are E or Z; however, a mixture of stereoisomers will be obtained (unless sterics – usually ring strain – prevent it).

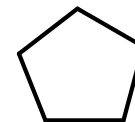


# Strategies for Making Cyclopentanes



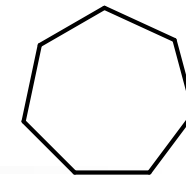
- Cyclopentane rings are most often formed using a one-bond disconnection approach similar to that on page 3.
  
- In this case, the nucleophilic carbon and the electrophilic carbon are in the same molecule and separated by three carbon atoms:
  
  
  
  
  
  
  
  
  
  
  
  
- Cyclopentane ring formation is favoured both kinetically and thermodynamically.

# Strategies for Making Cyclopentanes



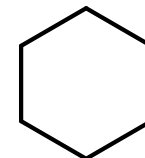
- Two-bond disconnections are usually not productive for cyclopentane rings.
  - In theory, we might be able to do a [4+2] cycloaddition of an allyl anion with an alkene, but the product is not favourable. Why not?
  - In theory, we might be able to do a photochemical [2+2] cycloaddition of an allyl cation with an alkene, but the product is not favourable. Why not?

# Strategies for Making Cycloheptanes



- Like cyclopentanes, cycloheptanes are best approached using a one-bond disconnection.
- In this case, the nucleophilic carbon and the electrophilic carbon are on the same molecule and separated by five carbon atoms:
  
- Cycloheptane ring formation is less favoured than cyclopentane or cyclohexane formation, but it is still relatively easy from both kinetic and thermodynamic perspectives.

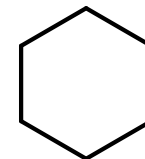
# Strategies for Making Cyclohexanes



- A wide variety of methods for making six-atom carbocycles (cyclohexanes, cyclohexenes, etc.) have been developed.
- By this point in the course, you have already learned about:
  - Diels-Alder reactions. Your text does an excellent job reviewing a variety of factors concerning regioselectivity, stereoselectivity and stereospecificity of Diels-Alder reactions. Since you learned this material in CHEM 2600, we will not dwell on it in class, but you should still read this section of the text.
  - Robinson annelations.

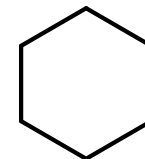


# Strategies for Making Cyclohexanes



- As with the other carbocycles, we can plan a one-bond disconnection using a functional group oriented approach.
- In this case, the nucleophilic carbon and the electrophilic carbon are on the same molecule and separated by four carbon atoms:

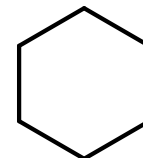
# Strategies for Making Cyclohexanes



- Cyclohexanes and cyclohexenes are unique in that they can also be accessed via benzene rings.
- Hydrogenation of a benzene ring is possible. It usually requires:
  - a more active catalyst than Pd/C (e.g. Pt, Ru, Rh or Ni-based catalysts),
  - higher-than-ambient pressures of hydrogen gas, and/or
  - heat
- If you planned to hydrogenate a benzene ring to a cyclohexane ring, what should you watch out for?



# Strategies for Making Cyclohexanes



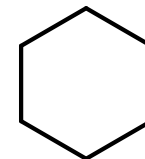
- It is also possible to reduce a benzene ring to the corresponding 1,4-cyclohexadiene ring using a reaction called a **Birch reduction**:
  
- This is particularly useful if the benzene has an alkoxy group attached since it generates an enol ether which can be hydrolyzed to give a cyclohexenone:





# Strategies for Making Cyclohexanes

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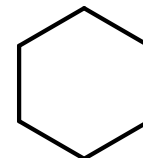


- Electron-donating groups result in the most highly substituted Birch reduction product possible given the substituent pattern:



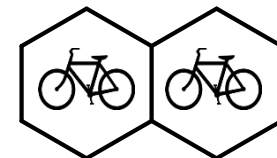
# Strategies for Making Cyclohexanes

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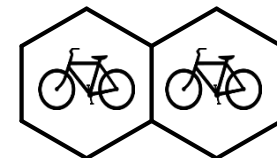
- Electron-withdrawing groups result in the least highly substituted Birch reduction product possible given the substituent pattern:

# Strategies for Making Bicycles

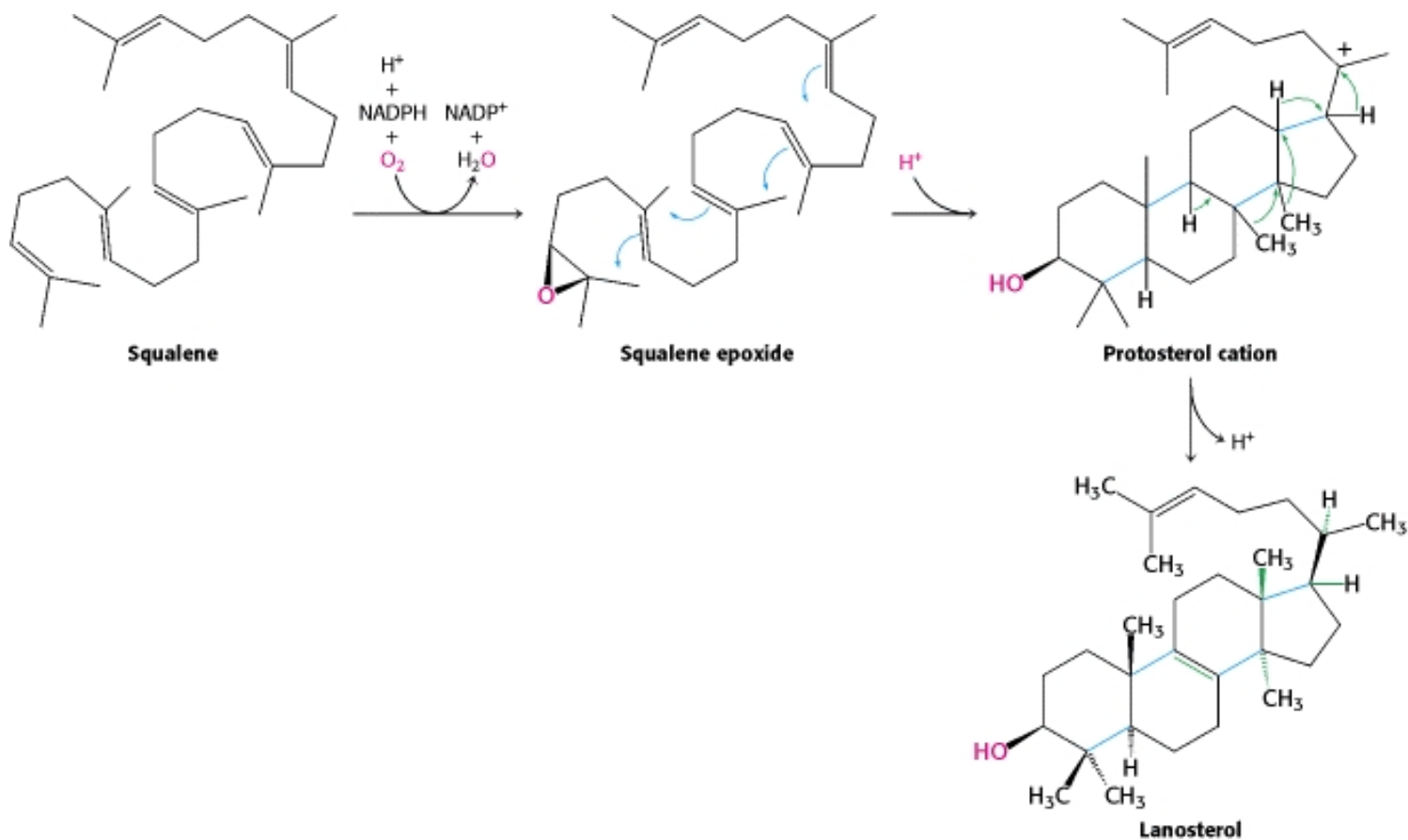


- According to a skeleton-based approach to retrosynthesis (disconnect into the simplest pieces), the best places to propose disconnections in a bicyclic structure are the *exendo* bonds (bonds which are exocyclic to one ring but endocyclic in the other):
  
- These are precisely the bonds formed in a Robinson annelation:

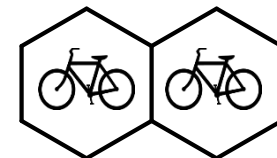
# Strategies for Making Bicycles



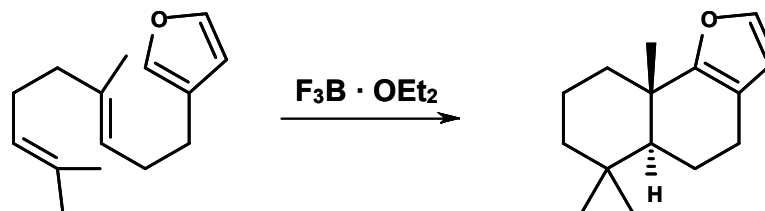
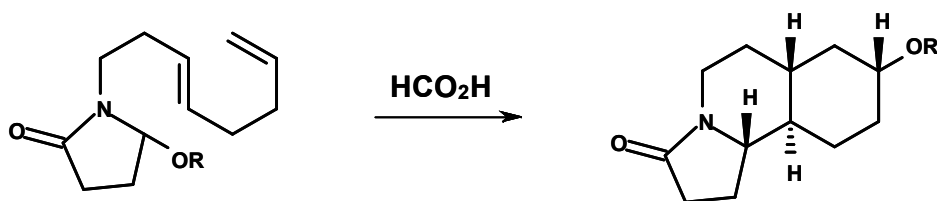
- These are also the bonds formed in bicyclization reactions such as the ones nature uses to construct steroids and other polycyclic biomolecules:



# Strategies for Making Bicycles

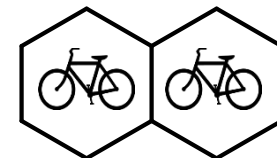


- Chemists take inspiration from nature when they propose similar cyclization reactions:



- As seen in the examples above, these reactions are often acid-catalyzed (Brønsted acid or Lewis acid). What sorts of challenges must be considered in such an approach?

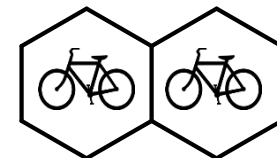
# Strategies for Making Bicycles



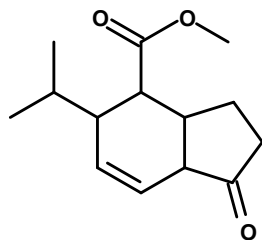
- We can also consider intramolecular Diels-Alder reactions as routes to bicyclic systems containing a cyclohexene ring (or a cyclohexane ring generated by hydrogenation of a cyclohexene ring).
- It is usually best if there are other functional groups present to activate the diene and/or dienophile. Recall that we usually want:
  - Electron donating groups attached to the diene, and/or
  - Electron withdrawing groups attached to the dienophile.(though inverse electron demand Diels-Alder reactions are possible).
- An intramolecular Diels-Alder approach will involve formation of an *endoendo* bond (C-C bond in both rings).



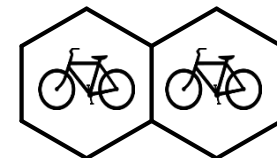
# Strategies for Making Bicycles



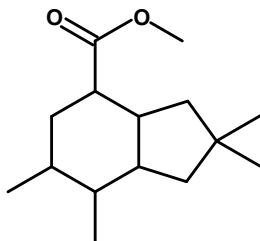
- If the target molecule still contains the cyclohexene C=C bond, use that to guide your disconnections.
- How could an intramolecular Diels-Alder reaction be used to construct the ring system in the molecule below:



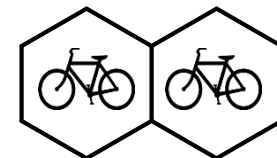
# Strategies for Making Bicycles



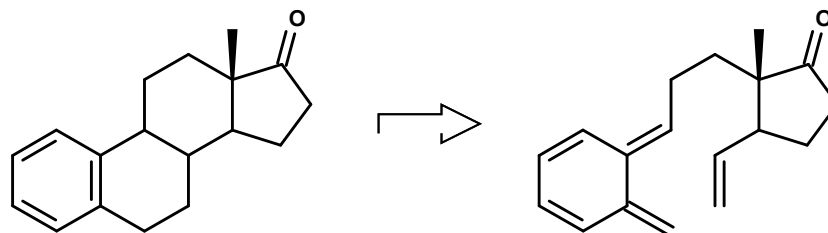
- If the target molecule does not contain the cyclohexene C=C bond, choose a convenient location for one and plan to hydrogenate the C=C bond later in the synthesis.
- How could an intramolecular Diels-Alder reaction be used to construct the ring system in the molecule below:



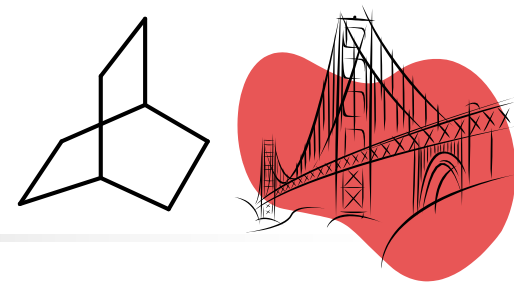
# Strategies for Making Bicycles



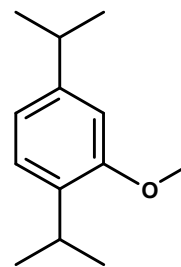
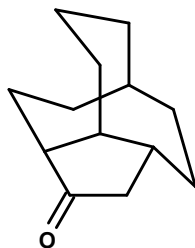
- Even complex molecules like steroids can be broken down into synthetically simpler pieces using a retrosynthesis based on an intramolecular Diels-Alder reaction at a key step:



# Bridged Ring Systems

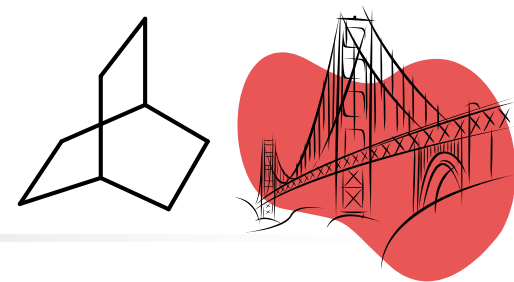


- When rings are fused to give a bridged system, the synthetic challenge usually increases. Most of us would find it much easier to propose a synthesis for the molecule on the right than the molecule on the left even though they have the same molecular formula:



- When evaluating disconnections on a bridged ring system like this, a couple of guidelines can help:
  - Avoid intermediates with medium-sized rings (8-13 atoms); they are strained (so, not thermodynamically favoured) but too large to be kinetically favoured.
  - Reduce the number of bridges. Bridges add complexity. Ideally, retrosynthesis leads to simpler pieces.

# Bridged Ring Systems



- To help with following these guidelines, the following procedure is often helpful:
  - Find the ring that is fused to the most other rings. It is likely best to disconnect one of its bonds.
  - Check each bond to see if its disconnection will lead to a medium-sized ring. Eliminate any bonds that do from consideration.
  - Draw the products of each remaining disconnection and choose the one that appears simplest.

